

REMARKS

Applicants respectfully request reconsideration of the present application in view of the reasons that follow.

I. Request for Clarification of the Status of the Claims

The Office Action Summary lists claims 14-110 pending, claims 39-50, 105 and 106 allowed, and claims 14-38, 51-104, and 107-110 as rejected, but this information is incorrect. First, claims 77-92, which were withdrawn from consideration in response to a restriction requirement, were cancelled by the amendment filed August 19, 2004, and acknowledged by the examiner in the Office action dated November 19, 2004, at page 2. Second, claim 97 is listed as allowed on page 6 of the Office action, but the Office Action Summary does not also list the claim as allowed and instead lists it as rejected. Finally, claims 16, 25, 33, 38, 63, 76, 94, 96, and 97 are neither explicitly rejected nor allowed in the Office action.

Applicants respectfully request the status of the claims be corrected and clarified. Specifically, claims 14-76 and 93-110 are pending, claims 39-50, 97, 105, and 106 stand allowed, and claims 14, 15, 17-24, 26-32, 34-37, 51-62, 64-75, 77-93, 95, and 107-110 stand rejected. Applicants understand claims 16, 25, 33, 38, 63, 76, 94, and 96 to be neither rejected nor allowed and respectfully request clarification. *See* MPEP § 707.07(d).

II. Summary of the Claimed Invention

The claimed invention, as amended, is directed to bioadhesive compositions of nanoparticulate active agents and methods of using the same. The active agent particles, or liquid droplets comprising active agent, have an effective average particle size of less than about 4 microns.

In a first embodiment, the compositions comprise: (a) a water-soluble or poorly water-soluble crystalline nanoparticulate active agent; and (b) at least one cationic primary surface stabilizer (claims 14-26, 98, 101, and 102). These compositions do not comprise a phospholipid.

In a second embodiment, the compositions comprise: (a) water-soluble or poorly water-soluble active agent particles which are in a liquid state at or near room temperature; and (b) at least one cationic primary surface stabilizer, wherein the active agent particles are dispersed in a liquid medium in which they are poorly soluble (claims 27-50 and 103-106).

In a third embodiment, the compositions comprise: (a) active agent dissolved or dispersed in liquid droplets of a water-soluble or poorly water-soluble liquid; and (b) at least one cationic primary surface stabilizer adsorbed to the surface of the liquid droplets, wherein the liquid droplets are dispersed in a liquid medium in which they are poorly soluble (claims 51-76, 99, and 107-110).

Finally, the invention encompasses methods of using the nanoparticulate active agent compositions of the invention. A first and second method encompass applying a nanoparticulate active agent formulation to a biological surface. The active agent particles of the first method can be in a semi-crystalline state, an amorphous state, a mixture of crystalline and semi-crystalline, a mixture of crystalline and amorphous, or a mixture of crystalline, semi-crystalline, and amorphous (claim 93 and 94). The active agent particles of the second method are in a crystalline state (claims 95 and 96). The compositions of these two methods do not comprise a phospholipid. A third method encompasses applying a nanoparticulate composition comprising agriculturally active agent particles to plant tissue.

The claimed invention satisfies a need in the art for effective, stable compositions having excellent adhesion properties to biological surfaces. The term "bioadhesion" refers to any attractive interaction between two biological surfaces or between a biological and a synthetic surface. In the case of bioadhesive nanoparticulate active agent compositions, the term bioadhesion is used to describe the adhesion between the nanoparticulate active agent compositions and a biological substrate (i.e., gastrointestinal mucin). Application at page 13, lines 26-29. Surprisingly, the bioadhesive property of the compositions of the invention diminishes as the particle size of the active agent increases. Id.

The bioadhesive nanoparticulate active agent compositions are useful in any situation in which it is desirable to apply an active agent to a biological surface. For example, the

bioadhesive nanoparticulate active agent compositions of the invention can be used in pharmaceuticals, including biologics such as proteins and peptides, organic compounds, such as therapeutic small molecules, agricultural agents, cosmetic agents, hair compositions, and others. The bioadhesive nanoparticulate active agent compositions of the invention coat the targeted surface in a continuous and uniform film which is invisible to the naked human eye.

The bioadhesive compositions can be applied to any plant or animal surface. The adhesion exhibited by the inventive compositions means that the active agent nanoparticles are not easily washed off, rubbed off, or otherwise removed from the biological surface for an extended period of time.

III. Claim Rejections Under 35 U.S.C. § 103

A. Pace et al., U.S. Patent No. 6,177,103

Claims 14, 15, 17-21, 23, 24, 26, 27, 29-32, 34, 36, 37, 51, 52, 54-59, 61, 62, 64, 66-72, 74, 75, 93, 95, 101-104, and 107-110 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Pace et al., U.S. Patent No. 6,177,103 (“Pace”). Office Action at pages 2-3. Applicants respectfully traverse this ground of rejection.

1. Summary of Pace

According to the Examiner, Pace “teaches preparing a nanoparticulate composition of less than 2000 nm by adsorbing a cationic agent onto the surface of active agent particles . . .” Office Action at page 4.

Pace refers to submicron particles of water-insoluble compounds, particularly drugs, prepared by simultaneously stabilizing microparticulate suspensions of the compounds with surface modifier molecules by rapid expansion into an aqueous medium from a compressed solution of the compound and surface modifiers in a liquefied gas. *See* Abstract and col. 5, lines 14-21, of Pace. Examples of suitable surface modifiers include cationic surfactants. The objective of Pace is to “develop a process with high productivity based on the use of liquefied gas solvents, including supercritical fluid technology, that yields surface modifier stabilized suspensions of water insoluble drugs . . .” Pace at col. 4, lines 63-67.

2. The Invention of Claims 14-26, 95, 96, 98, 101, and 102

The invention of claims 14-26, 95, 96, 98, 101, and 102 is directed to a bioadhesive nanoparticulate active agent composition and a method of applying such a composition to a biological surface. The composition comprises a water-soluble or poorly water-soluble nanoparticulate active agent, which is in a crystalline state, and at least one cationic primary surface stabilizer. These compositions do not comprise a phospholipid.

i. Pace Teaches Amorphous Active Agent Particles, in Contrast to the Crystalline Active Agent Particles of the Claimed Invention

In contrast to the claimed invention, Pace fails to teach *crystalline* particles and instead teaches *amorphous* particles. The examiner attempts to overcome this deficiency by arguing that the present application does not disclose any criticality or unexpected results making the substitution of crystalline particles for amorphous particles obvious. However, these arguments fail to establish a *prima facie* case of obviousness. Specifically, the examiner has not established any motivation to substitute crystalline particles for the amorphous particles of Pace.

ii. Pace Teaches Away from the Use of Crystalline Active Agent Particles

In fact, Pace teaches away from the use of crystalline nanoparticles. For example, Pace states that “[a] rapid intimate contact between the surface modifier and the newly formed particle substantially inhibits the crystal growth of the newly formed particle.” *See e.g.*, col. 4, lines 38-40 of Pace. In addition, the method of Pace requires “very fast precipitation” (col. 4, line 31) and “very rapid precipitation” (col 4, line 33). Very rapid precipitation is the preferred way to produce amorphous particles, primarily because the phase transition (from solution to solid) is too rapid for the active agent molecules to organize themselves into a coherent crystal lattice.

This characteristic of “very fast precipitation” is well-known in the art as demonstrated by Reverchon *et al.*, INT. J. PHARMACEUTICS, 243:83-91 (2002) (Exhibit A). Specifically, Reverchon discloses a process by which small particles of the drug rifampicin

are precipitated from solution with supercritical solvents. Reverchon abstract. The rifampicin used was crystalline before processing but amorphous after processing. Reverchon at 88. Reverchon concludes that “[t]his difference can be explained by the very fast precipitation that can characterize the [semi-continuous supercritical antisolvent] that does not allow the organization of the compound in a crystalline form.” Thus, it was well-known in the art that “very fast precipitation” necessarily forms amorphous particles.

Accordingly, Pace does not teach or suggest the use of crystalline particles active agent particles, particularly as this reference teaches away from such a combination. *See* MPEP §§ 2143.02, 2143.02, 2145.X.D.2.

iii. The Examiner’s “lack of criticality” Argument Fails to Address the Deficiencies of Pace

The examiner alleged that the present application fails to state any criticality in using crystalline compared to amorphous particles to establish obviousness, but this argument is misplaced. The existence of criticality can overcome a *prima facie* case of obviousness, but the lack of criticality does not create the required motivation to combine prior art references needed to establish a *prima facie* case of obviousness. In other words, the lack of criticality does not establish a *prima facie* case of obviousness when motivation to achieve all elements of the claimed invention is lacking. For at least these reasons, claims 14-26, 95, 96, 98, 101, and 102 are not obvious in view of Pace.

2. The Invention of Claims 27-38, 103, and 104

The invention of claims 27-38, 103, and 104 is directed to a bioadhesive nanoparticulate active agent composition comprising “poorly water-soluble active agent particles which are in a liquid state at or near room temperature” and at least one cationic primary surface stabilizer. The active agent particles are dispersed in a liquid medium in which they are poorly soluble, and the nanoparticulate composition adsorbs to a biological surface.

Applicants previously argued that Pace fails to teach compositions comprising *liquid* particles but rather teaches only *solid* particles. In response the Examiner alleged that

Applicants have the burden to show that Pace does not teach particles that are in a liquid state at or near room temperature. Applicants have done so. Specifically, the x-axes on Figures 1 and 2 of Pace are labeled "Solid Particles," and Pace makes use of the words "precipitated" and "precipitation" in several places (col. 4, lines 20, 31, 33, and 52) and also the terms "rapid nucleation" (col. 5, line 34) and "particle agglomeration" (col. 5, line 49). These words are specific to solid forms. For example, solids rather than liquids are "precipitated." Furthermore, the examples disclose only fenofibrate and cyclosporine particles, both of which are solids at room temperature. Thus, one of ordinary skill in the art would understand Pace to teach solid particles and not liquid particles.

Withdrawal of this ground for rejection against claims 27-38, 103, and 104 is respectfully requested.

3. The Invention of Claims 51-63, 107, and 108

The invention of claims 51-63, 107, and 108 is directed to a bioadhesive nanoparticulate active agent composition comprising active agent dissolved or dispersed in liquid droplets of a poorly water-soluble liquid and at least one cationic surface stabilizer adsorbed to the surface of the droplets. The liquid droplets comprising active agent are dispersed in a liquid medium in which they are poorly soluble.

i. Pace Fails to Teach or Suggest Droplets Comprising Active Agent Dispersed in a Liquid Medium in Which they are Poorly Soluble

Pace fails to teach or suggest droplets comprising active agent dispersed in a liquid medium in which they are poorly soluble. The examiner cites col. 5, lines 43-47, and Example 1 as support for the conclusion that Pace teaches the claimed invention. However, these passages, nor any other portion of Pace, do not teach or suggest that droplets are formed. Instead, these passages teach that the water insoluble substance may be dissolved in a liquefied gas before being expanded into an aqueous dispersion. There is no teaching or suggestion that the expansion results in the formation of droplets containing the water insoluble substance, which are dispersed in the aqueous medium.

ii. Pace Fails to Teach or Suggest Droplets Having a Surface Modifier Adsorbed to the Surface Thereof

Even if droplets were formed, they would not have surface modifiers adsorbed on the surface, because the surface modifiers of the Pace invention “are chosen to be active at the compound-water interface” (Pace at col. 3, lines 63-67) and not at the liquid-liquid interface. Thus, the surface modifiers of Pace would be present on the compounds and not at the interface of the droplets, which are liquid, and the liquid medium the droplets are dispersed in, as required by the claims. In fact, Pace emphasizes that “[t]he principle feature of [Pace] is believed to be rapid attainment of intimate contact of the dissolved drug and the surface modifier....” Pace at col. 4, l. 30-33. Accordingly, Pace itself teaches against compositions having a surface modifier adsorbed to the surface of droplets comprising active agent.

Thus, withdrawal of this ground for rejection against claims 51-63, 107, and 108 is respectfully requested.

4. The Invention of Claims 64-76, 109, and 110

The invention of claims 64-76, 109, and 110 is directed to compositions comprising active a dispersed in liquid droplets of a water-soluble liquid.

Pace fails to teach active agents dispersed in liquid droplets of *a water soluble liquid*. As previously stated, Pace describes making particulate compositions using liquefied gas solvents, including supercritical fluid technology. Examples of useful liquefied gases are described at col. 6, lines 6-33, of Pace. None of the liquefied gasses are “water soluble,” because in the process of Pace, the compressed solution of the compound and surface modifiers in a liquefied gas are expanded into an aqueous medium. Such expansion is not possible if the liquefied gas is soluble in water (*i.e.*, an aqueous medium). Accordingly, Pace fails to teach active agents dispersed in liquid droplets of *a water soluble liquid*, as required by the claimed invention.

Moreover, Pace does not teach the formation of droplets nor does Pace teach the formation of droplets with cationic surface stabilizer “adsorbed to the surface of the liquid droplets,” as discussed above in Section III.A.3.ii.

Thus, for at least these reasons Pace fails to teach or suggest the invention of claims 64-76, 109, and 110, and, therefore, withdrawal of this ground for rejection is respectfully requested.

B. Pace in Combination with Liversidge et al., U.S. Patent No. 5,145,684

Claims 22, 28, 35, 47, 53, 60, 65, and 73 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Pace in combination with Liversidge et al., U.S. Patent No. 5,145,684 ("Liversidge"). Office Action at page 3. Applicants respectfully traverse this ground for rejection.

According to the Examiner, "Pace does not expressly teach that the composition further comprises an excipient or that water is used as the dispersion medium. Liversidge teaches that such composition can further comprise a carrier (excipient) and that the dispersion medium can be water." Office Action at page 3.

1. Liversidge Fails to Remedy the Deficiencies of Pace

Liversidge does not remedy the deficiencies of Pace, noted above in Section III.A. Specifically, neither Pace nor Liversidge teach compositions comprising particles, which are *liquids* at or near room temperature; rather, these references teach only *solid* particles. In addition, neither Pace nor Liversidge teach active agents dispersed in liquid droplets of a *water soluble liquid*. A combination of references that fails to teach all claim limitations cannot form a *prima facie* case of obviousness. See MPEP § 2143.03.

2. There is no Motivation to Combine Pace and Liversidge

Moreover, there is no motivation to combine the teachings of Pace and Liversidge. In fact, Pace and Liversidge teach away from such a combination. As discussed in detail above, Pace teaches a process for preparing amorphous compounds. For example, the method of Pace requires "very fast precipitation" (col. 4, line 31) and "very rapid precipitation" (col 4, line 33). A skilled artisan understands "very rapid precipitation" to form an amorphous compound.

In contrast, Liversidge teaches milling a *crystalline* drug. *See* Liversidge at col. 3, lines 32-37. Liversidge goes so far as to distinguish other methods suitable for amorphous drugs and describes the method as useful for preparing crystalline drug compositions rather than amorphous compositions. *See id.* (“The drug substance exists as a discrete crystalline phase. The crystalline phase differs from a non-crystalline or amorphous phase which results from a precipitation technique....”). Thus, Pace and Liversidge are diametrically opposed with one teaching a method for preparing amorphous compounds and one teaching a method of preparing crystalline compounds.

Accordingly, there is no motivation to combine the references. For at least these reasons, withdrawal of this ground for rejection is respectfully requested.

C. Pace in Combination with Cutie, U.S. Patent No. 5,891,420

Claims 98-100 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Pace in combination with Cutie, U.S. Patent No. 5,891,420 (“Cutie”). Office Action at page 6. Applicants respectfully traverse this ground for rejection.

According to the Examiner, “Cutie teaches that triamcinolone acetonide is a known anti-inflammatory.” Office Action at page 4.

This reference does not address the deficiencies of Pace, detailed above. For at least these reasons, withdrawal of this ground for rejection is respectfully requested.

IV. Conclusion

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a

check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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